IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#17

In Re: U.S. Patent 4,621,077

Issued: November 4, 1986

To: Sergio Rosini and Giorgio Staibano

Assignee: Istituto Gentili S.p.A.

For: PHARMACOLOGICALLY ACTIVE BIPHOSPHONATES, PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS THEREFROM

Assistant Commissioner for Patents
Box Patent Extension
Washington, D.C. 20231

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

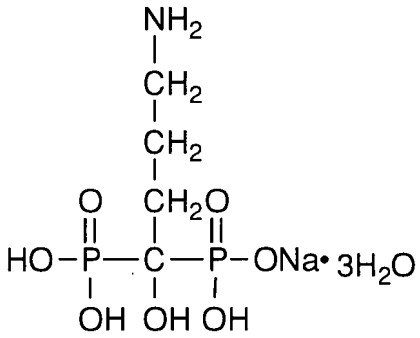
Sir:

Your Applicant, Istituto Gentili S.p.A., a company organized and existing under the laws of the Republic of Italy, represents that it is the assignee of the entire interest in and to Letters Patent of the United States 4,621,077 granted to Sergio Rosini and Giorgio Staibano on the 4th day of November, 1986 for PHARMACOLOGICALLY ACTIVE BIPHOSPHONATES, PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS THEREFROM by virtue of an assignment in favor of Istituto Gentili S.p.A. recorded June 8, 1984, Reel 4271, Frame 0756. By the Power of Attorney enclosed herein (Attachment A), Applicant appoints Merck & Co., Inc. a corporation organized and existing under the laws of the State of New Jersey, the exclusive licensee of the assignee of the entire interest in and to Letters Patent of the United States 4,621,077, as its agent to act in its interest in this matter, and Applicant also appoints Joseph DiPrima, Melvin Winokur and Joanne M. Giesser as attorneys of Istituto Gentili S.p.A. with regard to this application for extension

of the term of U.S. Patent 4,621,077 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Applicant hereby submits this application for extension of patent term under 35 U.S.C. §156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. 1.740). For the convenience of the Patent and Trademark Office, the information contained in this application will be presented in a format which will follow the requirements of Section 1.740 of Title 37 of the Code of Federal Regulations.

(1) The approved product FOSAMAX® contains alendronate sodium, chemically described as 4-amino-1-hydroxybutane-1,1-biphosphonic acid monosodium salt trihydrate, also called 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid monosodium salt trihydrate. Its structural formula is:



(2) The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act Section 505 (21 U.S.C. §355).

(3) The approved product FOSAMAX® received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act on September 29, 1995.

(4) The only active ingredient in FOSAMAX® is alendronate sodium, which has not been approved for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act prior to the approval of NDA 20-560 by the Food and Drug Administration on September 29, 1995.

(5) This Application for extension of patent term under 35 U.S.C. §156 is being submitted within the permitted 60 day period pursuant to 37 C.F.R. 1.720(f), said period which will expire on November 28, 1995.

(6) The complete identification of the patent from which extension is being sought is as follows:

Inventors: Sergio Rosini and Giorgio Staibano
Patent Number: 4,621,077
Issue Date: November 4, 1986
Expiration Date: November 4, 2003 (17 years from issue date)

(7) A copy of the patent is attached. (Attachment B)

(8) No terminal disclaimer has been issued. No Certificate of Correction or Re-examination Certificate has been issued. Enclosed is a copy of the receipt verifying payment of maintenance fees in 1989 and 1994 (Attachment C). Further enclosed is a copy of a statement under 37 C.F.R. 1.28(c) correcting the 1989 and 1994 maintenance fee payments to reflect large entity status by the Assignee Istituto Gentili S.p.A. (Attachment D).

(9) U.S. Patent 4,621,077 ("077") claims a method of using FOSAMAX®. Claim 1 of the "077" patent claims a method of use as follows:

> 1. A method of treatment of urolithiasis and inhibiting bone resorption which consists of administering to a patient in need thereof an effective amount of 4-amino-1-hydroxybutane-1, 1-biphosphonic acid.

This claim reads on a method of using the approved product FOSAMAX®. The active ingredient of FOSAMAX®, alendronate sodium, is a specific inhibitor of bone resorption. Alendronate sodium is chemically described as 4-amino-1-hydroxybutane 1, 1-biphosphonic acid monosodium salt trihydrate or 4-amino-1-hydroxbutylidene 1, 1-bisphosphonic acid monosodium salt trihydrate. Alendronate sodium is water soluble and *in vivo* yields alendronate, the active inhibitor of bone resorption. Thus the use of FOSAMAX® falls within the scope of Claim 1 of the "077" patent, and a claim of patent infringement could reasonably be asserted if a person not licensed by the patentee or exclusive licensee engaged, or induced a person to engage, in the use of FOSAMAX®.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) Investigational New Drug Application (IND 32,033) for alendronate sodium was filed August 29, 1988 and became effective on September 29, 1988.

New Drug Application (NDA 20-560) for FOSAMAX® (alendronate sodium) was submitted on March 31, 1995.

New Drug Application (NDA 20-560) for FOSAMAX® (alendronate sodium) was approved on September 29, 1995.

(11) As a brief description of the activities undertaken by Applicant Merck & Co., Inc., during the applicable regulatory review period, attached hereto is a chronology of the major communications between the Applicant and the FDA from August 29, 1988 to September 29, 1995. (Attachment E)

(12)(i) Applicant is of the opinion that U.S. Patent 4,621,077 is eligible for extension under 35 U.S.C. §156 because it satisfies all requirements for such extension as follows:

(a) 35 U.S.C. §156(a) -- U.S. Patent 4,621,077 claims a method of using the product FOSAMAX®.

(b) 35 U.S.C. §156(a)(1) -- U.S. Patent 4,621,077 has not expired before submission of this application.

(c) 35 U.S.C. §156(a)(2) -- The term of U.S. Patent 4,621,077 has never been extended under 35 U.S.C. §156(e)(1).

(d) 35 U.S.C. §156(a)(3) -- The application for extension is submitted by Applicant's agent, acting on behalf of the Applicant, who is the assignee, in accordance with the requirement of paragraphs (1) through (4) of 35 U.S.C.§156(d) and rules of the Patent and Trademark Office.

(e) 35 U.S.C. §156(a)(4) -- The product FOSAMAX® has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. §156(a)(5)(A) -- The commercial marketing or use of the product FOSAMAX® after regulatory review period is the first permitted commercial marketing or use under the provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C.355) under which such regulatory review period occurred.

(g) 35 U.S.C. §156(c)(4) -- No other patent has been extended for the same regulatory review period for the product FOSAMAX®.

(12)(ii) The length of the extension of patent term of U.S. patent 4,621,077 claimed by Applicant is 3.75 years or 1369 days. The length of the extension was determined pursuant to 37 C.F.R. §1.775 as follows:

(a) The regulatory review period under 35 U.S.C. §156(g)(1)(B) began on September 29, 1988 and ended on September 29, 1995, which is a total of 2556 days or 7.00 years, which is the sum of (1) and (2) below:

(1) The period of review under 35 U.S.C. §156(g)(2)(B)(i), the "Testing Period", began September 29, 1988 and ended on March 31, 1995, which is 6.50 years, or 2374 days; and

(2) The period of review under 35 U.S.C. §156(g)(2)(B)(ii), the "Application Period", began on March 31, 1995 and ended on September 29, 1995, which is 0.5 years, or 182 days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in sub-paragraph (12)(ii)(a) above (2556 days) less:

(1) The number of days in the regulatory review period which were on or before the date on which the patent issued (November 4, 1986) which is zero (0) days; and

(2) The number of days during which applicant did not act with due diligence, which is zero (0) days; and

(3) One half the number of days determined in sub-paragraph (12)(ii)(a)(1) after the patent issued (one half of 2374 days) which is 1187 days;

(c) The number of days as determined in sub-paragraph (12)(ii)(b) (1369 days) when added to the original term of the patent (November 4, 2003) would result in the date August 4, 2007;

(d) Fourteen (14) years when added to the date of NDA approval (September 29, 1995) would result in the date September 29, 2009;

(e) The earlier date as determined in sub-paragraphs (12)(ii)(c) and (12)(ii)(d) is August 4, 2007;

(f) Since U.S. Patent 4,621,077 issued after September 24, 1984 the period of extension may not exceed five (5) years. Five (5) years when added to the original expiration date of the patent (November 4, 2003) would result in the date November 4, 2008.

(g) The earlier date as determined by sub-paragraph (12)(ii)(f) and (12)(ii)(f) is August 4, 2007.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon this application is to be charged to the Deposit Account of Merck & Co., Inc., as authorized in the attached letter (Attachment F), which is submitted in duplicate. The requisite declaration pursuant to 37 C.F.R. §1.740(b) is attached hereto.

(15) All correspondence and inquiries may be directed to the undersigned, whose address and telephone number are given below.

Respectfully submitted,

By _____
Melvin Winokur
Reg. No. 32,763
Attorney for Applicants

Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0907
(908) 594-7234

Date: 11/20/95
Attachments:

Power of Attorney (Attachment A)
U.S. Patent 4,621,077 (Attachment B)
Copy of Receipt for Maintenance Fee Payment (Attachment C)
Copy of Statement 37 C.F.R. 1.28(c) (Attachment D)
Chronology of Regulatory Period (Attachment E)
Deposit Account Authorization (Attachment F)

CERTIFICATION

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. 156 including its attachments and supporting papers is being submitted as one original and triplicate copies thereof.

Melvin Winokur

Date: November 20, 1995

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent 4,621,077

Issued: November 4, 1986

To: Sergio Rosini and Giorgio Staibano

Assignee: Istituto Gentili S.p.A.

For: PHARMACOLOGICALLY ACTIVE BIPHOSPHONATES, PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS THEREFROM

Assistant Commissioner for Patents
Box Patent Extension
Washington, D.C. 20231

DECLARATION ACCOMPANYING
APPLICATION UNDER 35 U.S.C. §156 FOR EXTENSION OF PATENT TERM

I, MELVIN WINOKUR do hereby declare:

I am a patent attorney authorized to practice before the United States Patent and Trademark Office and I have general authority from the exclusive licensee Merck & CO., Inc in patent matters. Merck & Co., Inc has authority from the Patent Assignee, Istituto Gentili to act on its behalf in this application. I have also been authorized and appointed as attorney by the Assignee Istituto Gentili to transact all business in regard to this application for extension of the term of US patent No. 4,621,077 in the United States Patent and Trademark Office.

I have reviewed and understand the contents of the accompanying application being submitted pursuant to 37 C.F.R.§1.740.

I believe that the patent is subject to extension pursuant to §1.710.

I believe that an extension of the length claimed is justified under 35 U.S.C. 156 and the applicable regulations.

I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in §1.720.

Respectfully submitted,

By _____

Melvin Winokur
Reg. No. 32,763
Attorney for Applicants

Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0907
(908) 594-7234

Date: November 20, 1995

ATTACHMENT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent 4,621,077

Issued: November 4, 1986

To: Sergio Rosini and Georgio Staibano

Assignee: Istituto Gentili SpA

For: PHARMACOLOGICALLY ACTIVE BISPHOSPHONATES, PROCESS FOR THE PREPARATION THEREOF, AND PHARMACEUTICAL COMPOSITIONS THEREFROM

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

AUTHORIZATION OF AGENT AND
POWER OF ATTORNEY

Istituto Gentili S.p.A., a company organized and existing under the laws of the Republic of Italy, and having its registered office at via Mazzini 112, 56100 Pisa, Italy, enrolled in the Registry of Companies of Pisa Tribunal at Nr. 2022, being the owner of record of the above-identified U.S. Letters Patent, hereby authorize and appoint, Merck & Co., Inc., a corporation organized and existing under the laws of New Jersey and having its head office at One Merck Drive, P O Box 100, Whitehouse Station, New Jersey 08889-0100, and the Patent Attorneys named below:

Joseph F. DiPrima	(Reg. No. 28,944)
Melvin Winokur	(Reg. No. 32,763) and
Joanne M. Giesser	(Reg. No. 32,838)

all being employees of Merck & Co., Inc., individually and collectively to be the agents and attorneys of Istituto Gentili S.p.A. with regard to an application for extension of the term of U.S. Patent 4,621,077 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Please address all communications in the above matter to:

Melvin Winokur
Patent Counsel
Merck & Co., Inc.
126 E. Lincoln Avenue
Rahway, New Jersey 07065-0907

ISTITUTO GENTILI S.p.A.

By:

Name: Dr. Francesco De Rosa

Title: Managing Director

Date: 8 NOV. 1995

ATTACHMENT B

United States Patent [19]

Rosini et al.

[11] **Patent Number: 4,621,077**

[45] **Date of Patent: Nov. 4, 1986**

[54] **PHARMACOLOGICALLY ACTIVE BIPHOSPHONATES, PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS THEREFROM**

[75] Inventors: **Sergio Rosini; Giorgio Staibano**, both of Pisa, Italy

[73] Assignee: **Istituto Gentili S.p.A.**, Pisa, Italy

[21] Appl. No.: **618,578**

[22] Filed: **Jun. 8, 1984**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 480,264, Mar. 30, 1983.

[30] **Foreign Application Priority Data**

Apr. 15, 1982 [IT] Italy 20781 A/82

[51] **Int. Cl.**[4] **A61K 31/66**

[52] **U.S. Cl.** **514/108**

[58] **Field of Search** 424/204; 514/108

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,442,604	5/1969	Smith et al.	424/204
3,962,432	6/1976	Schmidt-Dunker	424/204
4,054,598	10/1977	Blum et al.	424/204
4,137,309	1/1979	Van Duzee	424/204
4,216,211	8/1980	Francis	424/204
4,216,212	8/1980	Flora et al.	424/204
4,230,700	10/1980	Francis	424/204
4,254,114	3/1981	Triebwasser	424/204
4,264,582	4/1981	Flora et al.	424/204
4,275,059	6/1981	Flora et al.	424/204
4,282,214	8/1981	Flora et al.	424/204
4,309,364	1/1982	Bentzen et al.	424/204
4,330,530	5/1982	Baker	424/204
4,330,537	5/1982	Francis	424/204
4,371,527	2/1983	Bentzen et al.	424/204

FOREIGN PATENT DOCUMENTS

57-154131	3/1982	Japan	424/204
7308017	12/1973	Netherlands	424/204
2096889	10/1982	United Kingdom	424/204

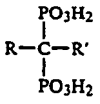
OTHER PUBLICATIONS

Chem. Abstract 96:52503t.
Chem. Abstract 100:175062g.
Chem. Abstract 88:170246u.
Fleisch, et al., *Europ. J. Clinical Invest.*, vol. 1, pp. 12–18 (1970).
Bassett et al., *The Yancet*, p. 845 (1969).
Francis, *Calc. Tiss. Res.*, 3, pp. 151–162 (1969).
Russell et al., *Calc. Tiss. Res.*, 6, pp. 183–196 (1970).

Primary Examiner—Albert T. Meyers
Assistant Examiner—F. Abramson
Attorney, Agent, or Firm—Bucknam and Archer

[57] **ABSTRACT**

Biphosphonic acids of general formula I:



(I)

in which R is a fluorine atom of a linear or branched alkyl radical containing between 1 and 5 carbon atoms, which may also be substituted by one or more amino groups of fluorine atoms or both amino groups and fluorine atoms, R' is hydroxy or fluorine, and their salts with an alkali metal, an organic base or a basic aminoacid, exhibit valuable properties in the treatment of urolithiasis or in the treatment as inhibitors of bone reabsorption. The compound 4-amino-1-hydroxybutan-1,1-biphosphonic acid is between 100 and 300 times more active than Cl_2MDP.

1 Claim, No Drawings

ATTACHMENT C

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
000178

BUCKNAM & ARCHER
600 OLD COUNTRY ROAD
GARDEN CITY, NY 11530

DATE MAILED
11/15/89

085439

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STA
1	4,621,077	273	245	----	06/618,578	11/04/86	06/08/84	04	YES	PAI

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If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
	BA-19650

PAYOR NUMBER
000178

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

75N5/0412

BUCKNAM & ARCHER
600 OLD COUNTRY ROAD
GARDEN CITY, NY 11530

DATE MAILED
04/12/94

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	S
1	4,621,077	284	935	----	06/618,578	11/04/86	06/08/84	08	YES	P

128

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR ATTY DKT

ATTACHMENT D

STATEMENT UNDER 37 C.F.R. 1.28 (c)
FOR THE PURPOSE OF CORRECTING DEFICIENCY
IN THE PAYMENT OF MAINTENANCE FEES IN USP 4,621,077

FERNANDA M. FIORDALISI certifies as follows:

1. I am a patent attorney and my Registration No. in the United States Patent and Trademark Office is 20,938.

2. Enclosed herein is a check in the amount of $1,800 to cover the deficiency in the amount of the Maintenance Fees paid in connection with USP 4,621,077 ("077"). The total amount of $1,800 has been calculated as the sum of $745.00 to correct the deficiency in connection with the maintenance fee due after three years and $1,055 to correct the deficiency in the maintenance fee due after seven years from the date of issuance of the patent.

3. The facts are as follows:

The Patent Application Serial No. 618,578 was filed on June 8, 1984 with an assignment from the inventors to Instituto Gentili S.P.A., (GENTILI) a corporation of Pisa, Italy. Correspondence between members of my firm and GENTILI were only through GENTILI's Italian Patent Attorneys, Studio Consulenza Brevettule in Milan, Italy, GENTILI's Italian patent attorneys.

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4. At the time the application was filed, and as late as July, 1986, when the final fees were paid, GENTILI was a small business entity entitled to pay one half government fees.

5. In 1989, I received instructions from Studio Consulenza Brevettuale to pay the maintenance fee due three years after the issuance of the patent. In 1994, I also received instructions from the same associate Studio Consulenza Brevettuale to pay the maintenance fee due seven years after the issuance of the patent.

6. On November 7, 1995, I was informed that in 1988 GENTILI granted a license to Merck & Co. on the '077, patent. By the terms of the license, GENTILI was responsible for maintaining the patent. I was not aware of, nor informed, that this license was in force at the time the prior maintenance fees were made.

7. In view of the fact that Merck & Co. is a large business entity, it is clear that the maintenance fees in 1989 and 1994 should have been paid at the rate due by a large business entity. Based on the above license agreement Merck & Co., had no duty to pay the maintenance fee.

8. I believe that the above errors occurred in good faith and were probably due to the failure of GENTILI to appreciate the requirements for a small business entity under United States law and also probably the poor knowledge of the English language by a clerical employee.

9. I submit that there was no intent to deceive on the part of the licensor Instituto Gentili.

Fern M Fiordalı-
Fernanda M. Fiordalisi
Reg. No. 20,938

Date: 11/10/95

13h

APPLICANT: ISTITUTO GENTILI S.P.A.
SER. NO: 618,578
PATENT NO: 4,621,077
FOR: PHARMACOLOGICALLY ACTIVE BIOPHOSPHONATES, PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS

CASE: EA-19650

PLEASE ACKNOWLEDGE RECEIPT OF THE FOLLOWING DOCUMENTS BY STAMPING DATE BELOW AND RETURNING THIS CARD:

STATEMENT CORRECTING DEFICIENCY IN PAYMENT OF MAINTENANCE FEES; CHECK FOR $1,800 TO COVER FEE

PMC

PATENT MAINTENANCE DIVISION
NOV 13 95
PATENT & TRADEMARK OFFICE

RECEIVED
NOV 17 1995
BUCKNAM & ARCH

BUCKNAM AND ARCHER
600 OLD COUNTRY ROAD
GARDEN CITY, N.Y. 11530

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ATTACHMENT E

FOSAMAX™ (Oral Alendronate Sodium)
Chronology of Events

IND 32,033	NDA 20-560	DATE	EVENT
X		08/29/88	Original IND for oral MK-217 was submitted.
X		09/14/88	Questions received from FA regarding CMC.
X		10/18/88	MRL responses to 9/14/88 FDA questions regarding manufacturing and controls were submitted.
X		12/01/88	Questions received from FDA regarding preclinical and chemistry issues.
X		03/07/89	MRL responses to Agency comments received 12/1/88 were submitted.
X		09/26/89	FDA comments received regarding Protocol 013 (Bioavailability) which was submitted 4/27/89.
X		10/17/89	Safety and tolerability data, summary of ongoing Paget's study, genetic toxicity study summaries, and proposed 6-week study in early postmenopausal women were submitted in response to FDA request of 5/9/89.
X		10/30/89	First Annual IND Progress Report was submitted to FDA.
X		11/09/89	Responses to FDA comments received 9/26/89 were submitted
X		02/15/90	Development and Reproductive Toxicity package was submitted.
X		02/27/90	Genetic Toxicity package was submitted.
X		04/24/90	Teleconference with FDA regarding the ongoing two-year rat carcinogenicity study. Following a large number of deaths in the high dose group (7.5 mg/kg/day), MRL proposed lowering dose to 5 mg/kg/day; FDA confirmed that deaths would not invalidate study.
X		05/21/90	Minutes were submitted for 4/24/90 teleconference
X		06/27/90	Update on two-year rat carcinogenicity studies was submitted to the FDA; MRL proposed termination of high dose groups.
X		06/29/90	Written concurrence received from FDA regarding MRL's plan to terminate high dose groups in two-year rat carcinogenicity studies.
X		07/12/90	Submission of Protocol 026 (One year Dose-Ranging Study in Osteopenia) and supportive preliminary safety data (from ongoing 6-week oral study in early postmenopausal women) was made to the FDA for review.
X		07/20/90	Agency (Dr. Dutta) requested a meeting to discuss the 6-week study upon completion. He requested that Protocol 026 begin after this discussion.
X		08/10/90	Background package was submitted for the 8/22/90

FOSAMAX™ (Oral Alendronate Sodium)
Chronology of Events (continued)

IND 32,033	NDA 20-560	DATE	EVENT
			meeting with the FDA.
X		08/22/90	Meeting with FDA to discuss the Clinical Development program (Protocol 026) and safety profile of alendronate sodium; MRL agreed to provide results of six-week oral study before starting two-year prevention of bone loss or three-year osteopenia bone density studies.
X		09/12/90	Minutes of the 8/22/90 meeting were submitted.
X		11/12/90	As result of 8/22/90 meeting, Protocols 029 (two-year prevention of bone loss) and 035 (Phase III three-year osteopenia bone density) were submitted for FDA review; also submitted was preliminary report of six-week oral study (Protocol 014)
X		11/01/90	Second Annual IND Progress Report was submitted to FDA
X		11/12/90	Three year study for treatment of Osteoporosis (Protocol 035), two-year prevention study (Protocol 029), and results of six-week study (Protocol 014) were submitted for review
X		11/29/90	Background package was submitted for End-of-Phase II meeting on 12-17-90
X		12/04/90	In response to an FDA request, results of the carcinogenicity studies in rats were submitted
X		12/17/90	End-of-Phase II Conference was held with FDA to discuss the clinical development programs for osteoporosis and metastatic bone disease
X		02/08/91	Minutes of the 12/17/90 meeting were submitted
X		03/08/91	Endocrinologic and Metabolic Drugs Advisory Committee Meeting to discuss use of etidronate for treatment of osteoporosis
X		10/01/91	Overall Study Design of the Fracture Intervention Trial was submitted for review
X		10/09/91	Background package was submitted for the 10/24/91 FDA meeting to discuss the MK-217 developmental program
X		10/21/91	Information on preclinical bone biology was submitted as additional background for 10/24/91 developmental meeting
X		10/24/91	Developmental meeting held between the FDA and MRL to discuss the ongoing clinical program: potential extension of the Phase III studies from two to three years; the proposed Fracture Intervention Trial (F.I.T.) design; results of preclinical studies in animal models were also presented and discussed

FOSAMAX™ (Oral Alendronate Sodium)
Chronology of Events (continued)

IND 32,033	NDA 20-560	DATE	EVENT
X		10/30/91	Third Annual IND Progress Report was submitted to FDA
X		11/27/91	Protocol 051 (F.I.T.) was submitted
X		01/23/92	Dr. Dutta provided comments concerning the proposed F.I.T. trial. He suggested that the trial begin after the Advisory Committee discussed treatment of osteoporosis at the 5/7-8/92 meeting. MRL agreed to only screen patients until after the meeting.
X		02/11/92	Minutes of 10/24/91 developmental meeting held between the FDA and MRL were submitted.
X		03/10/92	MRL Position paper on "The Adequacy of FDA's 1985 Draft Guidelines for Clinical Evaluation of Agents Used in the Treatment or the Prevention of Osteoporosis" was submitted for review for possible discussion of the evaluation of agents at the May 7-8, 1992 Endocrinologic and Metabolic Drugs Advisory Committee.
X		03/17/92	FDA comments regarding Protocol 051 (F.I.T.) were received.
-	-	05/7-8/92	Endocrinologic and Metabolic Drugs Advisory Committee Meeting to discuss Osteoporosis Guidelines.
X		07/23/92	At FDA meeting, MRL agreed to extend the double-blind phase of the pivotal BMD endpoint trials from two to three years duration; MRL introduced the concept of the Spine Deformity Index (SDI) as a continuous measure of treatment effect on fracture risk; it was also agreed that MRL should submit completed preclinical reports to enable an early start to the review process.
X		08/13/92	Prevention Protocol 055 (E.P.I.C.) was submitted.
X		08/20/92	Minutes of 7/23/92 meeting held between the FDA and MRL were submitted.
		08/31/92	FDA requests received regarding manufacturing and control amendments which provided revised data for alendronate sodium tablets and (Didronel) etidronate disodium tablets (was submitted 05/11/91).
X		09/08/92	FDA requests received regarding manufacturing and control amendments which provided revised drug substance data (were submitted 02/25/91 and 06/25/92).
X		09/08/92	FDA comments received regarding Protocol 056 (was submitted 06/02/92) and Protocol 057 (was submitted 06/30/92).

FOSAMAX™ (Oral Alendronate Sodium)
Chronology of Events (continued)

IND 32,033	NDA 20-560	DATE	EVENT
X		09/10/92	The rationale for the E.P.I.C. dose selection was submitted
X		09/11/92	In a teleconference, Dr. Dutta, FDA Medical Officer, concurred with the dose selection in the E.P.I.C. study.
X		09/14/92	Updated in response to FDA request to include the probability of developing gastrointestinal ulcers, the C.I.B. was submitted.
X		10/05/92	Report was submitted addressing methods for validating bone mineral density in osteoporosis studies, to serve as background material for possible FDA meeting.
X		10/06/92	MRL responses to FDA comments (received 09/08/92) were submitted.
X		10/14/92	In follow up to a request from the FDA at the 07/23/92 meeting, MRL submitted information to support not doing a treatment study in established osteoporosis in primates (as being considered for the new guidelines).
X		11/02/92	Written communication received from the FDA disagreeing with the MRL statement (submitted 10/05/92) regarding the use of bone mineral density as a primary endpoint for pivotal trials in the treatment of osteoporosis
X		11/09/92	Fourth Annual IND Progress Report was submitted to FDA.
X		11/02/92	FDA meeting to discuss methods for validating bone mineral density as a clinical endpoint in osteoporosis studies.
X		11/20/92	Responses to FDA CMC requests received 09/08/92 were submitted.
X		12/02/92	Minutes of 11/02/92 meeting with FDA were submitted.
X		12/08/92	Multiple conversations took place between the FDA and MRL regarding the FDA draft guidelines for development of osteoporosis and the feasibility of a second treatment paradigm; the FDA stated that a second specie model was required.
X		12/10/92	Data to support the rationale for dose selection were submitted to the FDA.
X		01/07/93	FDA letter received requesting that MRL add a notation under the WARNING section of the C.I.B. regarding acute and chronic leukemia.
X		01/13/93	Proposed protocol for a second animal (cynomolgus monkeys) treatment study was submitted for FDA review and comment.

FOSAMAX™ (Oral Alendronate Sodium)
Chronology of Events (continued)

IND 32,033	NDA 20-560	DATE	EVENT
X		02/04/93	Package was submitted including further rationale for selection of bone mineral density as the primary outcome variable for clinical osteoporosis studies; also included was the Data Analysis Plan for Phase III studies.
X		03/01/93	Background information for 03/03/93 meeting was submitted.
X		03/03/93	FDA meeting held to discuss a second preclinical animal treatment model for osteoporosis.
X		03/31/93	MRL's response to the FDA's 01/07/93 request to revise the C.I.B. with reference to leukemia; information was submitted supporting MRL's decision to not include the warning.
X		04/13/93	MRL submitted responses to the FDA request of 08/31/92 regarding CMC issues.
X		04/22/93	MRL met with the FDA to discuss the clinical study endpoints and the overall statistical analysis plan for the data from the Phase III osteoporosis studies.
X		07/06/93	In teleconference, the FDA Medical Reviewer, Dr. Dutta, stated his preference to receive the two claims (Osteoporosis and Paget's Disease of Bone) simultaneously; he also agreed that there is no issue of leukemia/lymphoma with alendronate.
X		08/03/93	The FDA agreed that since studies in rats and baboons had been completed, it was not necessary to complete a second "treatment" model of osteoporosis in cynomolgus monkeys.
X		08/10/93	Background information was submitted to the FDA for meeting to be held 08/19/93 to discuss FOSAMAX™ CANDA.
X		08/19/93	FDA/MRL meeting held to discuss proposed CANDA.
X		09/10/93	The plan for obtaining and analyzing bone biopsy specimens for all clinical studies was submitted.
X		09/30/93	Background information was submitted regarding the validity of the Spine Deformity Index (SDI) as a continuous outcome measure in clinical trials of treatment modalities for osteoporosis.
X		10/29/93	Fifth Annual IND Progress Report was submitted to FDA.
X		11/24/93	MRL's comments regarding the revised draft "Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis" were submitted.
X		12/14/93	FDA comments received regarding a protocol (study of

FOSAMAX™ (Oral Alendronate Sodium)
Chronology of Events (continued)

IND 32,033	NDA 20-560	DATE	EVENT
			bone mineral density in postmenopausal osteopenic black women of African-American descent) was submitted 05/11/93.
X		12/17/93	FDA and MRL discussed the pending change in recommended dose; dose to be increased from 5 mg to 10 mg for the treatment of osteoporosis.
X		02/17/94	Written clarifications to the FDA minutes (received 01/05/94) of the FDA/MRL meeting held on 04/22/93 were submitted.
X		02/18/94	A summary of the results of the preliminary analysis of BMD data at the two-year time point from pivotal Phase III treatment studies (035 and 037); also submitted was data supporting MRL's decision to change the recommended therapeutic dose.
X		04/27/94	Complete animal data package on preclinical safety assessment and bone biology studies of alendronate were submitted; the package conformed to the format of the Item 5 section of the NDA and was intended to support the NDA.
X		05/10/94	The Safety Assessment CANDA (covering Pharmacology/Toxicology data was submitted to the IND on 04/27/94) was provided to the FDA reviewers to aid in the review.
X		05/23/94	The second year interim results of the Phase III osteoporosis studies (Protocols 035 and 037), vertebral endpoint report, and histomorphometry data were submitted.
X		06/07/94	A meeting was held with the FDA to discuss the results of the analysis of the two-year data for all endpoints from the osteoporosis clinical trials.
	X	07/25/94	Background Package was submitted for Pre-NDA Meeting scheduled for 8/9/94.
	X	08/09/94	A pre-NDA meeting was held to discuss the formatting of the three year clinical data and the content of the NDA submission providing for treatment of osteoporosis in postmenopausal women and Paget's disease of bone. Specific proposals regarding the statistical data analysis plan and the presentation of serious adverse experience information were agreed upon.
X		10/03/94	All available Clinical Pharmacology Study Reports were submitted to the agency for review.
	X	10/03/94	Background Information for Pre-NDA CMC meeting with the agency was submitted.

FOSAMAX™ (Oral Alendronate Sodium)
Chronology of Events (continued)

IND 32,033	NDA 20-560	DATE	EVENT
X		10/10/94	CMC information essentially identical to that which will be submitted to the NDA was submitted as a convenience to the reviewer to examine before the Pre-NDA CMC meeting to be held 10/18/94.
X		10/18/94	Pre-NDA CMC meeting held with the agency.
X		10/26/94	Sixth Annual IND Progress Report was submitted to FDA.
X		12/13/94	Agency questions received via FAX regarding preclinical data.
X		12/21/94	Additional agency questions received via FAX regarding preclinical data.
X		12/29/94	Initial responses to agency preclinical questions asked 12/13/94 were submitted.
	X	12/29/94	Pre-NDA Chemistry, Manufacturing and Controls (Item 3) was submitted.
X		01/17/95	The three-year results from the primary Phase III clinical trials were submitted.
X		02/16/95	Complete responses to agency preclinical questions asked 12/13/94 and 12/21/94 were submitted.
X		02/28/95	Background package for FDA /MRL meeting scheduled for 03/09/95 was submitted.
	X	03/02/95	A replacement page was submitted for the Pre-NDA Chemistry, Manufacturing and Controls section.
X		03/09/95	FDA/MRL meeting held to discuss 3-year results of the Primary Phase III trials and future supplemental applications.
	X	03/13/95	Dr. Hemwall discussed the timing of the FOSAMAX™ advisory committee date with Mr. Hedin (CSO).
	X	03/31/95	Complete NDA delivered to the FDA.
	X	04/07/95	Corrected User Fee Form was submitted.
	X	04/19/95	Corrected Volume 2.10 was submitted.
	X	05/01/95	Clarification on manufacturing sites and location of Ballydine, Ireland facility provided at FDA request.
	X	05/05/95	Biopharmaceutical data and Clinical Study Reports (CSRs) provided on diskette at FDA request.
	X	05/08/95	"90 day meeting" formally requested to discuss the upcoming Advisory Committee meeting.
	X	05/09/95	Questions from the reviewing pharmacologist, Dr. Barbehenn were received via phone conversation.
	X	05/11/95	Full CSR for Protocol 069 provided at FDA request.
	X	05/15/95	An overview of the upcoming Safety Update Report (SUR) provided at FDA request.
	X	05/23/95	Responses to pharmacology questions (received via telephone conversation 05/09/95) provided to FDA.

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Chronology of Events (continued)

IND 32,033	NDA 20-560	DATE	EVENT
	X	05/25/95	Responses to biostatistics questions (received via telephone conversations) provided to FDA.
	X	05/25/95	Responses to pharmacology questions (received via FAX communication 05/16/95) provided to FDA.
	X	05/31/95	Allocation schedules for Protocols 053, 065, and 069 provided at FDA request.
	X	06/01/95	Responses to pharmacology questions (received via FAX communication 05/23/95) provided to FDA.
	X	06/02/95	Responses to questions (received via telephone conversation 05/30/95) provided to FDA.
	X	06/02/95	Responses to biostatistics questions (received via FAX communication 05/24/95) provided to FDA.
	X	06/06/95	Draft background package for the July 13, 1995 Advisory Committee Meeting was submitted.
	X	06/07/95	Responses to biostatistics questions regarding urine volume data from Protocol 053 (received via FAX communication 05/31/95) provided to FDA.
	X	06/08/95	Responses to biopharmaceutical questions (received via FAX communication 05/04/95) provided to FDA.
	X	06/13/95	Meeting held between FDA and MRL to discuss the status of the NDA and the ongoing review.
	X	06/16/95	Responses to biostatistics questions regarding a breakdown of the vertebral fracture occurrences by study site (received at the FDA/MRL meeting 06/13/95) provided to FDA.
	X	06/20/95	Background package for the July 13, 1995 Advisory Committee Meeting was submitted.
	X	06/21/95	Case Report Forms (CRFs) from four clinical sites identified by the FDA were submitted to support the site inspections by the FDA.
	X	06/23/95	Addresses were clarified at FDA request to support the site inspections by the FDA.
	X	06/27/95	Responses to requests for additional pharmacokinetic and pharmacodynamic data to support the 30-minute interval between dosing and the first food or beverage (other than plain water) of the day (received at the FDA/MRL meeting 06/13/95) provided to FDA.
	X	06/28/95	Responses to biometrics questions regarding electronic files of animal carcinogenicity data (received via telephone conversation 06/23/95) provided to FDA.
	X	06/29/95	Desk copies of data reports were submitted as electronic files 06/28/95 were provided at FDA request.
	X	06/29/95	Responses to biopharmaceutical questions regarding

FOSAMAX™ (Oral Alendronate Sodium)
Chronology of Events (continued)

IND 32,033	NDA 20-560	DATE	EVENT
			information on tablet dissolution and batch records (received via telephone conversation 06/20/95) were provided to FDA.
	X	07/06/95	Responses to questions concerning the Environmental Assessment (received via FAX communication 06/23/95) were provided to FDA.
	X	07/06/95	Responses to pharmacology questions (received via telephone conversation 06/20/95 and 06/28/95) were provided to FDA.
	X	07/13/95	The Endocrinologic and Metabolic Drugs Advisory Committee Meeting reviewed FOSAMAX™.
	X	07/27/95	Revised Draft Labeling was submitted to the FDA.
	X	07/31/95	Safety Update Report was submitted to the FDA.
	X	07/31/95	Amended Draft Labeling was submitted to the FDA based on the Advisory Committee recommendations.
	X	08/01/95	Responses to questions concerning the Environmental Assessment (received via FAX communication 07/10/95) were provided to FDA.
	X	08/01/95	Responses to chemistry questions regarding clarification of terminology used in certain FDA documents (received via telephone conversation 07/26/95) were provided to FDA.
	X	08/03/95	Responses to request for clarification regarding reprocessing procedures described in the NDA (received via telephone conversation 08/01/95) were provided to FDA.
	X	08/07/95	Responses to pharmacology questions (received in person 07/27/95) were provided to FDA.
	X	08/07/95	Responses to chemistry questions regarding clarification of batch record keeping (received via telephone conversation 08/07/95) were provided to FDA.
	X	08/15/95	Revised Draft Labeling was submitted to the FDA based on agency recommendations.
	X	08/15/95	Responses to clinical questions regarding follow-up information on Paget's Disease patients treated with alendronate to further document the duration of remission and potential need for retreatment (received via telephone conversations 08/07/95 & 08/09/95) were provided to FDA.
	X	08/18/95	Teleconference held between FDA & MRL to discuss FOSAMAX™ labeling.
	X	08/21/95	Proposed revisions to Draft Labeling to include information to support preclinical labeling statements

FOSAMAX™ (Oral Alendronate Sodium)
Chronology of Events (continued)

IND 32,033	NDA 20-560	DATE	EVENT
			were submitted to the FDA as a result of discussions during 08/18/95 teleconference between FDA & MRL.
	X	08/21/95	Responses to chemistry questions (received via FAX communication 08/09/95) including a copy of the Updated Methods Validation Package were provided to FDA.
	X	08/22/95	Revised Draft Labeling was submitted to the FDA based on agreements between FDA & MRL at the teleconference held 08/18/95.
	X	08/23/95	A correction to the submission dated 08/21/95 was submitted to the FDA.
	X	08/28/95	Draft Package Circular and Draft Patient Package Insert (PPI) revised to include further input from the FDA were submitted.
	X	08/29/95	Responses to chemistry questions (received via telephone conversation 08/24/95) and a revised Updated Methods Validation Package were provided to FDA.
	X	08/30/95	Written confirmation was submitted of the agreement between the FDA & MRL following the receipt of FDA comments on 08/09/95 and conversations on 08/29/95 regarding the dissolution specifications for both the 10 mg and 40 mg tablets.
	X	08/31/95	A further revised PPI was submitted.
	X	09/08/95	Based on an FDA/MRL telephone conversation on 08/31/95, additional revisions were incorporated in the PPI and submitted.
	X	09/15/95	Following a telephone request from the FDA on 09/15/95, clarification regarding the submission of CRFs (hard copy and electronic) was provided to the FDA.
	X	09/29/95	Following an FDA/MRL teleconference on 09/28/95, Final Draft Labeling for the Package Circular and Patient Package Insert were submitted to the FDA
	X	09/29/95	FOSAMAX™ is approved by the FDA for the treatment of osteoporosis in postmenopausal women and for Paget's Disease of bone.

ATTACHMENT F

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent 4,621,077

Issued: November 4, 1986

To: Sergio Rosini and Giorgio Staibano

Assignee: Istituto Gentili S.p.A.

For: PHARMACOLOGICALLY ACTIVE BIPHOSPHONATES, PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS THEREFROM

Assistant Commissioner for Patents
Box Patent Extension
Washington, D.C. 20231

Sir:

Transmitted herewith is the application for extension of patent term under 35 U.S.C. § 156 with regard to U.S. Patent 4,621,077.

Please charge our Deposit Account No. 13-2755 in the amount of $1,060.00. The Commissioner is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Account No. 13-2755. Duplicate copies of this sheet are enclosed.

Respectfully submitted,

By _____
Melvin Winokur
Reg. No. 32,763
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Date: November 20, 1995

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